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(21) International Application Number: PCT/SE97/00676 (22) International Filing Date: 22 April 1997 (22.04.97) (30) Priority Data: 9601556-5 24 April 1996 (24.04.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): LUNDGREN, Anna [SE/SE]; Topeliusgatan 4, S-412 68 Göteborg (SE). STJERNFELT, Ulla [SE/SE]; Klintegatan 9, S-431 38 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: NEW PHARMACEUTICAL FORMULATION OF A THROMBIN INHIBITOR FOR PARENTERAL USE (57) Abstract A pharmaceutical formulation of a trombin inhibitor for parenteral use having an extended release effect.		

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NEW PHARMACEUTICAL FORMULATION OF A THROMBIN INHIBITOR FOR PARENTERAL USE

Field of invention

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The present invention relates to a new pharmaceutical formulation of thrombin inhibitors for parenteral use, which is an extended release formulation. The invention also relates to a process for the manufacture of such a formulation and, the use of the new formulation in medicine.

10

Background of the invention

Thrombin inhibitors are effective for treatment of a number of diseases characterized by hypercoagulation.

15

The compounds melagatran and inogatran are low- molecular weight, water-soluble thrombin inhibitors which are rapidly cleared from the body. To permit administration with a low dosing frequency an extended release formulation is desirable, especially when the administration is parenteral.

20

Parenteral extended release formulations allow a drug to be delivered in a dose resulting in a suitable plasma concentration for an extended period of time, with less frequent administration and avoiding high peak concentrations. An extended release effect may be a

prerequisite for subcutaneous or intramuscular treatment, particularly for low molecular weight, water soluble drugs with short half-life.

A wide range of means have been used to achieve parenteral extended release.

5

One approach has been to retard the diffusion of the drug out of the formulation.

Retardation can be obtained by using viscous vehicles, or by means of reversible complex formation to a constituent of the formulation.

10 Cyclodextrins are enzymatically modified starches made of glucopyranose units. In this process, three different cyclodextrins are formed, α -, β -, and γ -cyclodextrin with six, seven and eight glucopyranose units, respectively. The outer surface of the cyclodextrin is hydrophilic and the internal cavity is hydrophobic. Cyclodextrins are known to form inclusion complexes with compounds or parts of compounds that fit into the ring cavity and
15 are attracted to the hydrophobic environment. Cyclodextrins, and in particular β -cyclodextrins, have been used in many pharmaceutical formulations, e.g. to increase solubility and stability. In EP 149 197 the combination of a medicinal substance sparingly soluble in water and a partially etherified β -cyclodextrin is disclosed with the object of providing better solubility and stability.

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The object of achieving extended release of various water-soluble drugs from oral and oily parenteral formulations by cyclodextrin derivatives is disclosed in K. Uekama et al., Release control of water-soluble drugs by β -cyclodextrin derivatives. Minutes Int. Symp.

Cyclodextrines, 5th Ed. Sante, Paris, France 1990, pages 418-423, Conference Proceedings.

In WO 95/05197 the use of a cyclodextrin derivative for preparing an opioid analgesic preparation for intramuscular or subcutaneous administration is described. However, the problem of achieving extended release of parenteral formulations of water-soluble low molecular weight compounds from low viscosity cyclodextrin solutions has not been previously described.

Disclosure of the invention

It has now surprisingly been found that a formulation of a water solution of a thrombin inhibitor comprising a thrombin inhibitor which is melagatran, inogatran or a physiologically acceptable water-soluble salt thereof, and a cyclodextrin additive can be used for extending the release of the thrombin inhibitor in vivo after parenteral administration.

Melagatran is the compound $\text{HOOC-CH}_2\text{-(R)-Cgl-Aze-Pab}$ (disclosed in EP 701 568) and inogatran is the compound $\text{HOOC-CH}_2\text{-(R)-Cha-Pic-Nag}$ (disclosed in EP 618 926), wherein

Aze is (S)-azetidine-2-carboxylic acid

Cgl is (S)-cyclohexylglycine

Cha is (S)- β -cyclohexyl alanine

Nag is noragmatine

Pab is 1-amidino-4-aminomethyl benzene

Pic is (S)-pipecolinic acid.

Water solubility in this context is defined as a solubility of more than 3.5 g / 100 g of water, in accordance with the solubility definition of Martindale (Martindale, The Extra
5 Pharmacopea, The Pharmaceutical press, London 1993).

Physiologically acceptable salts, are such as for instance but not restricted to salts from inorganic and organic acids, e.g. hydrobromide, hydrochloride, sulphate, nitrate; salts of sulphonic acids, e.g. methane sulphonate, ethane sulphonate, benzene sulphonate, toluene
10 sulphonate, 'naphthalene-2-sulphonate, salts of carboxylic acids, e.g. maleate, benzoate, salicylate, salts of hydroxy acids, e.g. acetate, malate, succinate, gluconate, glycollate, lactate, tartrate, citrate, ascorbate, salts of fatty acids, e.g. hexanoate, octanoate, decanoate, undecylenate, dodecylsulphate, oleate, stearate.

15 The additive is a cyclodextrin which may be either unsubstituted α -cyclodextrin, β -cyclodextrin, or γ -cyclodextrin or substituted derivatives thereof.

Preferred unsubstituted cyclodextrin is the γ -cyclodextrin.

20 The preferred substituted cyclodextrins according to the present invention are alkylated cyclodextrins.

The preferred alkylated cyclodextrins are O-alkylated cyclodextrins having alkyl (1-5C) groups. The alkyl groups may be linear or branched, preferably linear with 1 to 4 carbon
25 atoms. The alkyl groups may be substituted by one or more hydroxy groups at position 2-5, preferably by a hydroxy group at the 2-position and/or the 3-position.

The most preferred alkyl group is the 2-hydroxypropyl.

The preferred of the hydroxypropyl substituted cyclodextrins are the hydroxypropyl- β -
5 cyclodextrins and the hydroxypropyl- γ -cyclodextrins. The most preferred are the
hydroxypropyl- β -cyclodextrins.

The alkylated cyclodextrin is usually not a homogenous product but a mixture of alkylated
10 cyclodextrin molecules with a various number of hydroxyl groups substituted.

The degree of substitution of the hydroxypropyl- β -cyclodextrins may theoretically vary
from 1 to 21 hydroxypropyl groups per β -cyclodextrin molecule, with a preferred average
degree of substitution in the range of 1 to 7. The most preferred average degree of
15 substitution is in the range of 2 to 4 hydroxypropyl groups per β -cyclodextrin molecule.

The concentration of the thrombin inhibitor is usually in the range 0.01 to 50% (w/w),
preferably 0.1 to 25% (w/w) of the ready to use formulation.

20 The concentration of cyclodextrin is 10 to 70 % (w/w) of the ready to use formulation.

The amount of thrombin inhibitor relative to the amount of cyclodextrin in the formulation
according to the invention varies in the range 1:7000 to 1:1 calculated by weight.

Due to physiological considerations the pH of the formulation is preferably adjusted to between 3 and 10. For pH adjustment an acid is used, such as but not restricted to acetic acid, citric acid, fumaric acid, hydrochloric acid, malic acid, nitric acid, phosphoric acid, propionic acid, sulfuric acid, tartaric acid, or an alkali, such as sodium hydroxide or any
5 other physiologically suitable alkalising agent.

The formulation may contain antimicrobial preservatives, tonicity modifiers and/or antioxidants.

10 The formulation may be prepared by dissolving the solid components in water, adjusting the pH and sterilizing the resulting solution. The order in which the components are dissolved and at which stage the pH adjustment or sterilization is performed is not critical, however, normally the sterilization is performed in the last step.

15 Suitable daily parenteral doses for the trombin inhibitor in the therapeutical treatment of humans are 0.001 to 50 mg/kg body weight, preferably 0.005 to 5 mg/kg.

The pharmaceutical formulation is suitable for prophylaxis and/or treatment in arterial as well as venous thromboembolism.

20

The formulation is to be used parenterally including intracutaneous, subcutaneous, intralipomateus, intramuscular and intraperitoneal administration.

Working examples

Example 1 [1.8% w/w (20 mg/ml) melagatran in 40% w/w of hydroxypropyl- β -cyclodextrin (HP β CD)]

5	Melagatran	7.97 g
	HP β CD	183.2 g
	HCl to adjust pH to 5	qs
	Adjust with water for inj. to	450.2 g

10 The cyclodextrin is weighed and dissolved during stirring in the main part of the water. The weighed amount of melagatran is then added to the cyclodextrin solution and dissolved during stirring. The pH of the dissolved solution is adjusted to 5 with 2 M HCl. The rest of the water is added to the final weight. The solution is sterilized by filtration through 0.22 μ m sterile filters and filled into sterile injection vials.

15

In a similar way the following formulations were prepared:

Example 2 [1.9% w/w (22 mg/ml) inogatran in 40% w/w of hydroxypropyl- γ -cyclodextrin (HP γ CD)]

20	Inogatran	0.329 g
	HP γ CD	6.88 g
	HCl to adjust pH to 7.4	qs
	Adjust with water for inj. to	17.52 g

Example 3 [1.7% w/w (20 mg/ml) melagatran in 50% w/w of HP β CD)

Melagatran	0.518 g
HP β CD	15.0 g
5 HCl to adjust pH to 5	qs
Adjust with water for inj. to	30.0 g

Extended release

A dose of 5 mg of melagatran was administered subcutaneously to humans in a) the
10 cyclodextrin formulation of Example 1, and b) in a physiological saline solution.

The data in the Table shows a 3-fold decrease in absorption rate and a reduced peak plasma concentration for the cyclodextrin formulation as compared to the physiological saline solution.

TABLEHuman data

	a) Cyclodextrin vehicle		b) Physiological saline vehicle	
	Time	Mean plasma concentration N = 6	Time	Mean plasma concentration N = 6
	(minutes)	($\mu\text{mole/litre}$)	(minutes)	($\mu\text{mole/litre}$)
5	5	- **	5	0.084
	10	- *	10	0.23
	15	- *	15	0.43
	20	0.24	20	- *
10	30	- *	30	0.59
	40	0.37	40	- *
	45	- *	45	0.55
	60	0.39	60	0.49
	90	0.38	90	0.37
15	120	0.32	120	0.28
	150	0.28	150	0.22
	180	0.23	180	0.19
	210	- *	210	0.15
	240	0.15	240	0.12
20	300	0.10	300	0.085
	360	0.063	360	- *
	480	0.031	480	0.024
	600	0.015	600	- *
	720	0.010	720	- *
25				
30				

The total area under the plasma concentration versus time curves are equal for the two

formulations ($\text{AUC} = 88.3 \mu\text{mole} \cdot \text{L}^{-1} \cdot \text{min.}$)

*) not determined

35 **) below limit of quantitation

Claims

1. An extended release formulation for parenteral administration of a water-soluble thrombin inhibitor comprising a thrombin inhibitor which is melagatran, inogatran or a physiologically acceptable water-soluble salt thereof and a water soluble cyclodextrin additive for extending the release of the thrombin inhibitor.
2. A formulation according to claim 1, wherein the cyclodextrin is a substituted cyclodextrin having alkyl-, or hydroxyalkyl groups.
3. A formulation according to claim 1, wherein the cyclodextrin is hydroxypropyl cyclodextrin.
4. A formulation according to any one of the preceding claims, wherein the cyclodextrin is hydroxypropyl- β -cyclodextrin or hydroxypropyl- γ -cyclodextrin.
5. A formulation according to any one of the preceding claims, wherein the cyclodextrin is 2-hydroxypropyl- β -cyclodextrin.
6. A formulation according to any one of the preceding claims, wherein the thrombin inhibitor is melagatran.

7. A formulation according to any one of the preceding claims, wherein the concentration of the thrombin inhibitor is in the range 0.01 to 50% (w/w) of the ready to use formulation.
8. A formulation according to any one of the preceding claims, wherein the concentration
5 of cyclodextrin is 10 to 70% (w/w) of the ready to use formulation.
9. A formulation according to any one of the preceding claims for use in the prophylaxis and/or treatment in arterial and/or venous thromboembolism in mammals including man.
- 10 10. A process for the preparation of a formulation according to any one of the preceding claims wherein the thrombin inhibitor and the cyclodextrin are dissolved in water, the pH is adjusted and the resulting solution is sterilized or the separate steps are performed in any other order.
- 15 11. A method for the prophylaxis and/or treatment of arterial and/or venous thromboembolism in mammals including man by administering to a host in need thereof of a formulation as defined in any of claims 1 to 9.
- 20 12. Use of a water-soluble thrombin inhibitor which is melagatran, inogatran or a physiologically acceptable water-soluble salt thereof and a cyclodextrin additive for extending the release of the thrombin inhibitor as defined in any one of claims 1 to 9 for the manufacture of an extended release medicament for prophylaxis and/or treatment of arterial and/or venous thromboembolism.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/00676

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 38/55, A61K 47/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI, IFIPAT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9505197 A1 (BORGBJERG, FINN, MOLKE), 23 February 1995 (23.02.95) --	1-11
A	EP 0149197 A2 (JANSSEN PHARMACEUTICA N.V.), 24 July 1985 (24.07.85) --	1-11
A	Chem. Pharm. Bull., Volume 38, No 1, 1990, A. Yoshida et al, "Utility of 2-Hydroxypropyl-beta-cyclodextrin in an Intramuscular Injectable Preparation of Nimodipine" page 176 - page 179 -- -----	1-11

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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Date of the actual completion of the international search

11 July 1997

Date of mailing of the international search report

01 -08- 1997

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/00676

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9, 11
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/07/97

International application No.

PCT/SE 97/00676

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9505197	A1	23/02/95	AU	7383094 A	14/03/95

EP	0149197	A2	24/07/85	SE	0149197 T3	
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